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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/672,020	09/29/2000	Thomas J. Gardella	0609.4820002/SRL/TBB	2982

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EXAMINER	
MURPHY, JOSEPH F	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 12/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/672,020	GARDELLA ET AL.	
	Examiner	Art Unit	
	Joseph F Murphy	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 10-42* is/are pending in the application.

4a) Of the above claim(s) *4-7 and 13-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 8, 10-12, 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Formal Matters

Claims 1-8, 10-42 are pending. Claims 4-7, 13-41 stand withdrawn from consideration pursuant to 37 CFR 1.142(b). Claims 1-3, 8, 10-12, 42 are under consideration.

Response to Amendment

The objection to claims 8-9 have been obviated by Applicant's amendment and are thus withdrawn.

Claim Rejections - 35 USC § 112 first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 8-12 stand rejected, and new claim 42 is rejected, under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polypeptide with the amino acid sequence as set forth in SEQ ID NO: 1, does not reasonably provide enablement for a biologically active variants of SEQ ID NO: 1 as set forth in claim 1, or polypeptides having an amino acid sequence at least 90% identical to SEQ ID NO: 1 or the variants set forth in claim 1, or fragments of SEQ ID NO: 1, or fragments of the variants of SEQ ID NO: 1, for reasons of record set forth in the Office Action of 6/19/2003. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue.

The rejection of record set forth that in the instant case, the claims encompass variants of SEQ ID NO: 1 as set forth in claim 1, polypeptides having an amino acid sequence at least 90% identical to SEQ ID NO: 1 or the variants set forth in claim 1, and fragments of SEQ ID NO: 1 or fragments of the variants of SEQ ID NO: 1 as set forth in claim 1. Thus, the claims encompass many variant proteins. Applicant has only taught the amino acid sequence of SEQ ID NO: 1. While the specification provides adequate guidance for making SEQ ID NO: 1, and provides adequate teaching on how to make other polypeptides with a similar sequence, the specification fails to provide guidance on use of the variant polypeptides. Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. For example, it is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. For example, Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes

the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph). It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. Thus, the amino acid sequence of a polypeptide determines its structural and functional properties, and predictability of which amino acids can be substituted is extremely complex and well outside the realm of routine experimentation, because accurate predictions of a polypeptide's structure from mere sequence data are limited. Since detailed information regarding the structural and functional requirements of the encoded proteins are lacking, it is unpredictable as to which polypeptide variations, if any, meet the limitations of the claims.

Applicants do not disclose any actual or prophetic examples on expected performance parameters of any of the possible muteins of SEQ ID NO: 1. Therefore, while the specification provides the necessary guidance to make the polypeptides set forth in SEQ ID NO: 1 and variants, it does not provide the necessary guidance for one of skill in the art to use the polypeptides. Further, since no functional language is associated with the polypeptides of SEQ ID NO: 1 or variants, one of ordinary skill in the art would not know how to use these defined sequences except in further characterization of the sequences themselves. Due to the large quantity of experimentation necessary to generate the large number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the

absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Applicant has amended the claims to recite that the encompassed polypeptides are biologically active. The Specification states that biological activity of the peptides refers to any biological activity of the polypeptide. Examples of these activities include, but are not limited to metabolic or physiologic function of compounds of SEQ ID NO: 1 or derivatives thereof including similar activities or improved activities or those activities with decreased undesirable side-effects. Also included are antigenic and immunogenic activities of said compounds such as for example, SEQ ID NO: 1 or derivatives thereof. However, the term "biological activity" is not clear as set forth in the rejection under 35 USC 112 second paragraph, infra. Thus the skilled artisan would not be apprised of the metes and bounds of the functional limitation with regard to SEQ ID NO: 1 activity. Applicant further argues that the Specification sets forth examples of biologically active peptides, and that ample guidance is provided as to which substitutions could be tolerated because the number of muteins encompasses is small. However, Applicant is required to enable one of skill in the art to make and use the claimed invention, while the claims encompass methods using polypeptides that the specification only teaches one skilled in the art to test for functional variants. It would require undue experimentation for one of skill in the art to make and use the claimed polypeptides, since the skilled artisan would have to first make polypeptide variants of SEQ ID NO: 1, then determine a function, then test for that function.

Because the amino acid sequence of a polypeptide determines its structural and functional properties, and predictability of which amino acids can be substituted is extremely complex, accurate predictions of a polypeptide's structure from mere sequence data are limited. Thus, since Applicant has only taught how to test for polypeptide variants of SEQ ID NO: 1, and has not taught how to make polypeptide variants of SEQ ID NO: 1, it would require undue experimentation of one of skill in the art to make and use the claimed polypeptides.

The rejection of record further set forth that Claim 12 encompasses a pharmaceutical composition of the polypeptide of claim 1, which encompasses variants of SEQ ID NO: 1 as set forth in the claim. However, as set forth supra, the specification does not provide the necessary guidance to make the polypeptides set forth in SEQ ID NO: 1 and variants, and it also does not provide the necessary guidance for one of skill in the art to use the polypeptides as a pharmaceutical composition. Applicant argues that PTH is a major regulator of calcium homeostasis, the disruption of which can produce many clinical disorders, and that PTH administration has been shown to promote bone formation. However, given that the claims encompass many variant proteins and given the lack of a clear function that the variant proteins must possess, it would require undue experimentation for one of skill in the art to make and use the claimed variant polypeptides as a pharmaceutical composition since the claims as written do not set forth a function that the claimed polypeptides must possess, so it is not clear how the skilled artisan would use the claimed peptides since they do not have to have any effect on the PTH-2 receptor on osteoblast cells.

Given the breadth of claims 1-2, 8-12 in light of the predictability of the art as determined by the number of working examples, the level of skill of the artisan, and the guidance provided

in the instant specification and the prior art of record, it would require undue experimentation for one of ordinary skill in the art to practice the claimed invention.

Claims 2, 8-12 stand rejected, and new claim 42 is rejected, under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for reasons of record set forth in the Office Action of 6/19/2003. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The rejection of record set forth that these are genus claims. The claims encompass polypeptides having an amino acid sequence at least 90% identical to SEQ ID NO: 1 or the variants set forth in claim1, and fragments of SEQ ID NO: 1 or fragments of the variants of SEQ ID NO: 1 as set forth in claim 1. Thus, the claims encompass variant proteins, while Applicant has only taught SEQ ID NO: 1. The specification and claim do not indicate what distinguishing attributes shared by the members of the genus. Thus, the scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification and claims do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general,

guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

Applicant has amended the claims to recite that the encompassed polypeptides are biologically active, and argues that the Specification sets forth examples of biologically active peptides, thus setting forth a representative number of the claimed genus. The Specification states that biological activity of the peptides refers to any biological activity of the polypeptide. Examples of these activities include, but are not limited to metabolic or physiologic function of compounds of SEQ ID NO: 1 or derivatives thereof including similar activities or improved activities or those activities with decreased undesirable side-effects. Also included are antigenic and immunogenic activities of said compounds such as for example, SEQ ID NO: 1 or derivatives thereof. However, the term "biological activity" is not clear as set forth in the rejection under 35 USC 112 second paragraph, infra. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide a correlation between structure and function, since no clear function is set forth for the

claimed polypeptides. Thus, no identifying characteristics or properties of the instant polynucleotides encoding polypeptides are provided such that one of skill would be able to predictably identify the molecules that would retain "biological activity" of variants of the SEQ ID NO: 1 polypeptides.

Claim Rejections - 35 USC § 112 second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2, 8, 10-12, 42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-2, 8, 10-12, 42 are vague and indefinite in the recitation of the term "biologically active". The term "biologically active" is not defined by the claim, and give no definition of what this activity is. Various biological activities can be attributed to a peptide. For example, "activity" could constitute transportation throughout a cell, alteration of tertiary structure due to changes in pH, ligand binding, or modulation of second messenger effect, etc. 'Activity' could also be referring to the ability of the fragment to stimulate antibody production. The Specification states that biological activity of the peptides refers to any biological activity of the polypeptide. Examples of these activities include, but are not limited to metabolic or physiologic function of compounds of SEQ ID NO: 1 or derivatives thereof including similar activities or improved activities or those activities with decreased undesirable side-effects. Also included are antigenic and immunogenic activities of said compounds such as for example, SEQ ID NO: 1 or derivatives thereof. In reviewing a claim for compliance with 35 U.S.C. 112,

second paragraph, the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. 112, second paragraph "by providing clear warning to others as to what constitutes infringement of the patent". MPEP 2173.02, MPEP 2173.02. In the instant case, the myriad of effects set forth as biological activities of the claimed polypeptide would not indicate to the skilled artisan of the metes and bounds of the claims.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph F. Murphy whose telephone number is 703-305-7245. The examiner can normally be reached on M-F 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 703-308-6564. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-0294 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Joseph F. Murphy, Ph. D.
Patent Examiner
Art Unit 1646
December 2, 2003

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